142. An Unexpected Transformation of Benzyl Carbamates into α-Azidobenzeneacetamides

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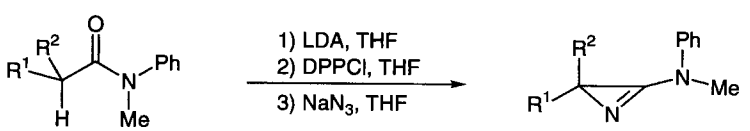
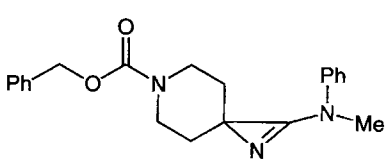
Successive treatment of benzyl carbamates **5** (Z-protected secondary amines) with lithium diisopropylamide (LDA), diphenyl phosphorochloridate (DPPCl), and NaN_3 yielded the corresponding α-azidobenzeneacetamides **6** in 45–50% yield (*Schemes 2* and *3*). In the case of Z-protected diisopropylamine **5b**, the phosphate **7** was isolated as a minor product. A reaction mechanism for this unexpected transformation is proposed in *Scheme 4*, the key step being the ring closure of a benzylic anion to give an oxirane intermediate **B**. In cursory experiments, it was demonstrated that α-azidobenzeneacetamides **6** can be used as 2-phenylglycine synthons in the formation of dipeptides by using a phosphine-mediated coupling (*Scheme 5*).

Introduction. – Recently, we have described a convenient synthesis of *N*-methyl-*N*-phenyl-2*H*-azirin-3-amines (3-amino-2*H*-azirines) [1–4]. Starting with enolizable *N*-methyl-*N*-phenylamides **1** of carboxylic acids, azirinamines **2** were prepared by consecutive treatment with lithium diisopropylamide (LDA), diphenyl phosphorochloridate (DPPCl), and NaN_3 (*Scheme 1*). In the case of the 2,2-disubstituted azirinamines **2** (R^1,$R^2 \neq H$), diphenyl phosphoroazidate (DPPA) could be used instead of DPPCl/NaN_3, whereas in the case of $R^2 = H$, reaction of the enolate of **1** and DPPA resulted in an α-amination [5] or a diazo transfer [6].

Scheme 1



1 **2**



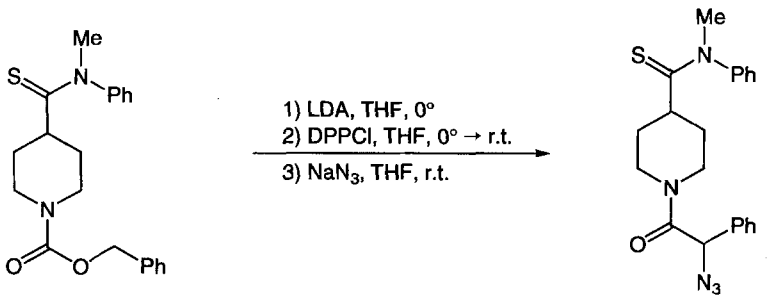
2a

[1]) Part of the Ph.D. thesis of *C.S.*, Universität Zürich, 1997.

Within the program of the synthesis of heterospirocylic azirinamines as synthons for heterocyclic α-amino acids [4], we tried to prepare the *N*-[(benzyloxy)carbonyl]-protected 1,6-diazabicyclo[2.5]oct-1-ene derivative **2a** as a synthon for 4-aminopiperidine-4-carboxylic acid.

Results and Discussion. – Following the protocol of the azirinamine synthesis (*cf.* [4]), a solution of benzyl 4-(*N*-methyl-*N*-phenylthiocarbamoyl)piperidine-1-carboxylate (**3**) in THF was treated with LDA at 0°. Then, DPPCl was added and, after stirring at room temperature for 24 h, the mixture was treated with excess NaN_3. After 3 days, no starting material **3** could be detected, and chromatographical workup gave azido derivative **4** in 47% yield (*Scheme 2*).

Scheme 2



3 **4**

The structure of **4** follows from spectral data and elemental analysis. In the IR spectrum, two strong absorption bands at 2100 and 1650 cm^{-1} are characteristic for the azido and amide group, respectively. The ESI-MS shows three main peaks at *m/z* 432, 416, and 394 corresponding to $[M + K]^+$, $[M + Na]^+$, and $[M + H]^+$, whereas in the EI-MS, *m/z* 351 ($[M - N_3]^+$) is the base peak. In the NMR spectra, the doubling of signals in (D_6)DMSO at 0° (*e.g.*, 5.52, 5.38 and 62.1, 61.9 ppm (Ph*CH*N_3), 3.60, 3.53 and 45.2, 45.1 ppm (MeN), 206.8, 206.5 ppm (CS), and 166.6, 166.2 ppm (CO)) indicate the presence of two conformers (rotamers); at 100°, the corresponding signals appear at 5.38 and 63.2, 3.60 and 45.3, 208.3, and 166.9 ppm.

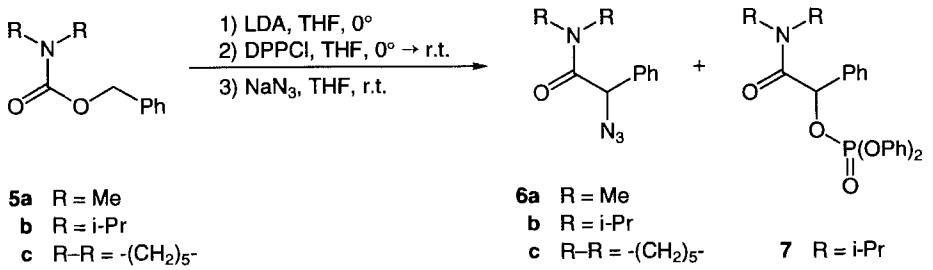
For testing the scope of the unexpected transformation **3** → **4**, we prepared the Z-protected secondary amines **5a**–**c** (*Scheme 3*) by standard methods using benzyl carbonochloridate (ZCl). Under the above mentioned conditions for the azirinamine synthesis, the α-azidobenzeneacetamides **6a**–**c** were formed as the main products [2]). Whereas in the case of **5a**, the starting material was completely consumed, 42 and 28% of **5b** and **5c**, respectively, were recovered. The yields of isolated **6a**–**c**, calculated with respect to consumed **5**, amounted to 45–50%. In the case of **5b**, phosphate **7** was isolated after chromatography as a by-product in 22% yield.

The structures of the azido-amides **6** were deduced from the spectral data and, in the case of **6b**, it was established by an X-ray crystal-structure determination (*Fig.*).

For the formation of **6** and **7**, we propose the reaction mechanism depicted in *Scheme 4*: Deprotonation at the benzyl position of **5** gives the anion **A** which, in the presence of DPPCl, cyclizes to give the oxiranyl phosphate **B**. This oxirane seems to be

[2]) Treatment of **5c** with LDA and diphenyl phosphorazidate (DPPA) also yielded **6c** (44%).

Scheme 3



5a R = Me
b R = i-Pr
c R–R = -$(CH_2)_5$-

6a R = Me
b R = i-Pr
c R–R = -$(CH_2)_5$-

7 R = i-Pr

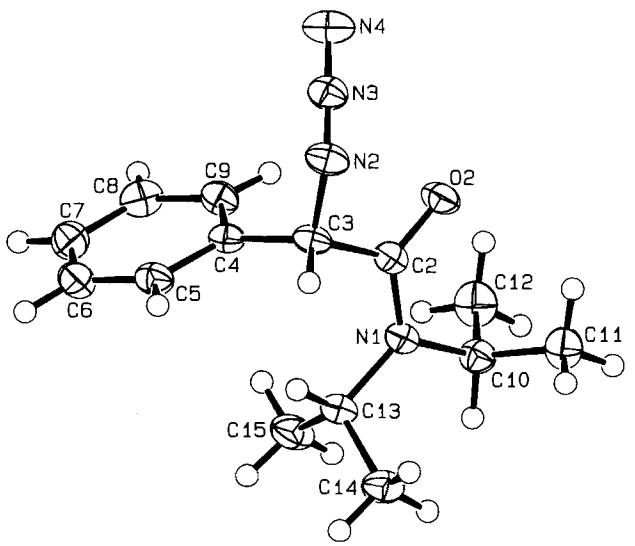
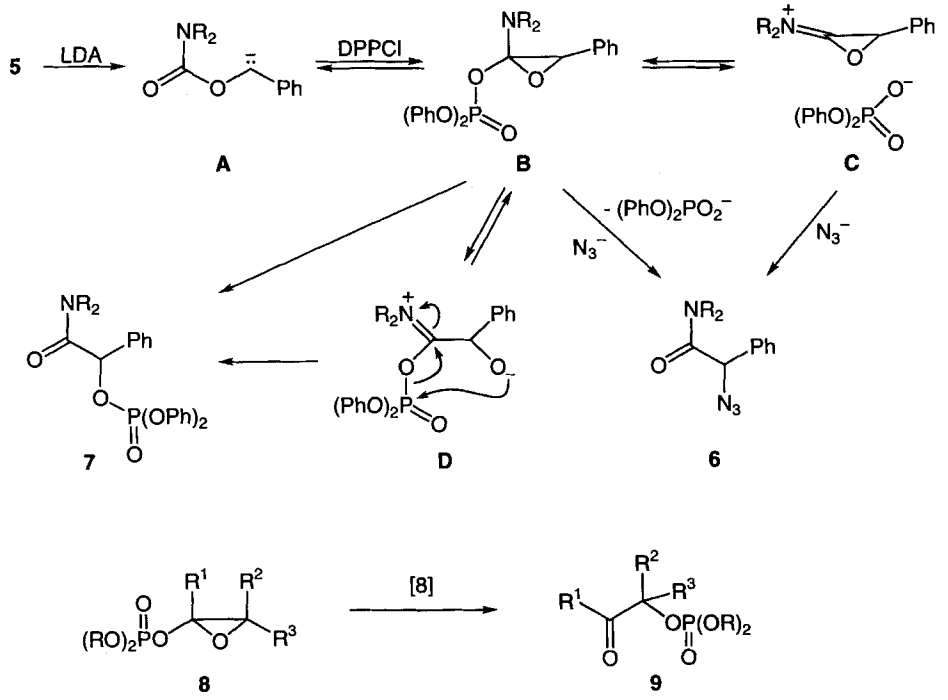


Figure. *ORTEP Plot* [7] *of the molecular structure of* **6b** (with 50% probability ellipsoids)

the crucial intermediate in the formation of the C–C bond between the carbamate C-atom and the benzyl C-atom. Opening of the oxirane ring by nucleophilic attack of N_3^- and elimination of diphenyl phosphate yields azido-amide **6**. A reaction mechanism with initial elimination of diphenyl phosphate from **B** to give the ion pair **C**, followed by ring opening of the oxiraneiminium by N_3^-, is also consistent with the results. Oxiranyl phosphate **B** is also a reasonable intermediate for the formation of **7**. The rearrangement of the phosphate group from C(2) to C(3) and concomitant opening of the three-membered ring leads to **7**. Alternative reaction mechanisms to the concerted rearrangement are the two-step mechanisms *via* the ion pair **C** followed by nucleophilic ring opening by the phosphate anion, and initial ring opening of **B** to give zwitterion **D** which undergoes a 1,4-phosphate shift, respectively. Phosphate **7** could also be a precursor of the azido-amide **6**, the latter being formed *via* a nucleophilic substitution of diphenyl phosphate by the azide ion.

There is a precedent for the rearrangement **B** → **7** described by *Adam et al.* [8]. Oxiranyl phosphates of type **8**, prepared by oxidation of enol phosphates with dimethyl-

Scheme 4



dioxirane or with peroxy acids, rearrange smoothly to give the corresponding 2-oxoalkyl phosphates **9** (*Scheme 4*).

In some preliminary experiments, the azido-amides **6a** and **6c** were tested as 2-phenylglycine (Gly(2Ph)) equivalents for the synthesis of glycyl-2-phenylglycine (Gly-Gly(2Ph)) derivatives. According to *Roberts* and coworkers [9] (*cf.* also [10] [11]), dipeptide esters are formed from α-azido esters and *N*-protected amino acids by using tertiary phosphines as reducing reagents. The reactive intermediates are iminophosphoranes generated from the azide and the phosphine (*cf.* [12]), and the coupling step most likely proceeds *via* a pentacoordinated P-intermediate [9].

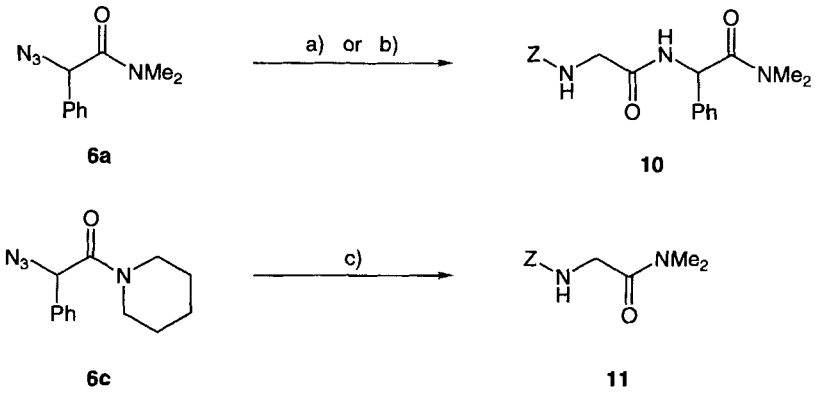
A solution of azido-amide **6a** and an equimolar amount of Bu_3P in toluene was stirred at room temperature for 4 h. After addition of Z-protected glycine (Z-Gly-OH) and heating to 80° for 8 h, the dipeptide derivative Z-Gly-Gly(2Ph)-NMe_2 (**10**, *Scheme 5*) was obtained in 57% yield[3]). The same product was prepared in 69% yield *via* catalytic reduction of the azido group of **6a** with H_2 (Pd/C) and coupling of the intermediate α-amino-*N*,*N*-dimethylbenzeneacetamide (Gly(2Ph)-NMe_2) and Z-Gly-OH using HBPyU[4]) and Et_3N.

With the aim to increase the yields by using more nucleophilic phosphines, we treated azido-amide **6c** with hexamethylphosphorous triamide under the conditions described

[3]) No reaction was observed when Ph_3P was used instead of the more nucleophilic Bu_3P.

[4]) *O*-(1*H*-Benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-bis(tetramethylene)uronium hexafluorophosphate.

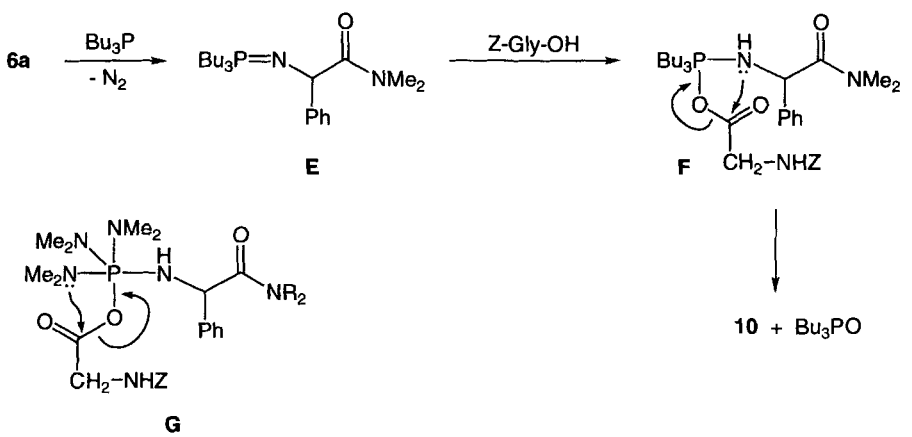
Scheme 5



a) 1. Bu_3P, toluene, r.t., 4h; 2. Z-Gly-OH, toluene, 80°, 8h.
b) 1. H_2, Pd/C, MeOH, r.t., 1h; 2. Z-Gly-OH, HBPyU, Et_3N, CH_2Cl_2, r.t., 16h.
c) 1. $(Me_2N)_3P$, toluene, r.t., 1h; 2. Z-Gly-OH, toluene, 80°, 8h.

above. Very surprisingly, we isolated the *N,N*-dimethylamide **11** of Z-protected glycine (Z-Gly-NMe_2) as the sole product of the reaction. This result, as well as the peptide coupling, can be rationalized by the same reaction mechanism (*Scheme 6*).

Scheme 6



As described in [9], the first intermediate is an iminophosphorane, *e.g.*, **E**, which reacts with the carboxylic acid to give the pentacoordinated P-compound **F**. The new peptide bond is then formed *via* an intramolecular acyl transfer in **F** and expulsion of tributylphosphine oxide. Using hexamethylphosphorous triamide, the pentacoordinated P-intermediate corresponding to **F** should be **G**, in which the acyl transfer to a dimethylamino group seems to be preferred.

We thank the analytical sections of our institute for spectra and elemental analyses and Dr. *A. Linden* for performing the X-ray crystal-structure determination. Financial support by the *Swiss National Science Foundation* and *F. Hoffmann-La Roche AG*, Basel, is gratefully acknowledged.

Experimental Part

General. See [4]. If not otherwise stated, IR spectra in $CHCl_3$, NMR spectra in $CDCl_3$ (^1H: 300 MHz; ^{13}C: 75.4 MHz), CI-MS with NH_3.

1. *Azido Derivatives* **4** *and* **6**. *1-(2-Azido-2-phenylacetyl)-*N*-methyl-*N*-phenylpiperidine-4-carbothioamide* (**4**). To a soln. of benzyl 4-(*N*-methyl-*N*-phenylthiocarbamoyl)piperidine-1-carboxylate (**3**; 1.820 g, 4.939 mmol) in THF (20 ml) at 0°, 2M lithium diisopropylamide (LDA) in THF (3.0 ml, 6.0 mmol) was added, and the mixture was stirred for 1 h. Then, diphenyl phosphorochloridate (DPPCl; 1.49 ml, 5.56 mmol) was added at 0°, the mixture stirred for 1 h at r.t., and NaN_3 (963 mg, 14.81 mmol) added. After stirring at r.t. for 4 h, the precipitate was removed by filtration. Evaporation and CC (SiO_2, hexane/AcOEt 2:1) of the residue yielded 887 mg (45.7%) of **4**. Pale yellow crystals. M.p. 110–112°. IR: 3060*w*, 3020*m* (sh), 3000*m*, 2960*m* (sh), 2920*w*, 2860*w*, 2100*s*, 1650*s*, 1595*w*, 1495*s*, 1470*m*, 1450*s*, 1390*m*, 1370*w*, 1355*m*, 1310*w*, 1270*m*, 1220*m*, 1190*m*, 1170*m*, 1120*m*, 1090*m*, 1040*w*, 1025*w*, 1000*w*, 990*w*, 960*m*, 930*w*, 910*w*, 880*w*, 700*s*, 660*m*, 630*m*. ^1H-NMR (300 MHz, (D_6)DMSO, 373 K): 7.5–7.3, 7.25–7.2 (2*m*, 10 arom. H); 5.38 (*s*, PhC*H*N_3); 4.1–3.95 (*t*-like, br., 2 H_{ax} of CH_2NCH_2); 3.60 (*s*, MeN); 2.75–2.65, 2.55–2.3 (2*m*, 2 H_{eq} of CH_2NCH_2, H–C(4)); 1.9–1.75, 1.55–1.45 (2*m*, CH_2CHCH_2). ^1H-NMR (600 MHz, (D_6)DMSO, 273 K; 2 conformers): 7.5–7.3 (*m*, 10 arom. H); 5.52, 5.38 (2*s*, PhC*H*N_3); 4.4–4.35, 3.65–3.55 (2*m*, 2 H_{ax} of CH_2NCH_2); 3.60, 3.53 (2*s*, MeN); 2.6–2.55, 2.3–2.15, 1.95–1.5, 1.2–1.15, 0.9–0.85 (5*m*, 2 H_{eq} of CH_2NCH_2, H–C(4), CH_2CHCH_2). ^{13}C-NMR (75.4 MHz, (D_6)DMSO, 373 K): 208.3 (*s*, C=S); 166.9 (*s*, C=O); 145.8, 135.2 (2*s*, 2 arom. C); 130.2, 129.2, 129.0, 128.7, 128.1, 126.0 (6*d*, 10 arom. CH); 63.2 (*d*, PhCHN$_3$); 46.4 (*d*, C(4)); 45.3 (*q*, MeN); 43.3 (*t*, CH_2NCH_2); 32.3, 32.0 (2*t*, CH_2CHCH_2). ^{13}C-NMR (150.9 MHz, (D_6)DMSO, 273 K; 2 conformers): 206.8, 206.5 (2*s*, C=S); 166.6, 166.2 (2*s*, C=O); 144.9, 134.3 (2*s*, 2 arom. C); 130.0, 129.2, 129.1, 129.0, 128.8, 128.6, 127.8, 127.7, 125.6, 125.5 (10*d*, 10 arom. CH); 62.1, 61.9 (2*d*, PhCHN$_3$); 46.0, 45.9 (2*d*, C(4)); 45.2, 45.1 (2*q*, MeN); 44.2, 44.1, 41.3, 41.2 (4*t*, CH_2NCH_2); 32.4, 31.7, 31.4, 31.2 (4*t*, CH_2CHCH_2). ESI-MS: 432 (12, $[M + K]^+$), 416 (100, $[M + Na]^+$), 394 (14, $[M + 1]^+$). EI-MS: 351 (100, $[M - N_3]^+$), 261 (28, $[M - PhCHN_3]^+$), 178 (45), 82 (49), 77 (49). Anal. calc. for $C_{21}H_{23}N_5OS$ (393.51): C 64.10, H 5.89, N 17.80; found: C 63.81, H 5.92, N 17.30.

*α-Azido-*N,N*-dimethylbenzeneacetamide* (**6a**). In analogy to the previous experiment, benzyl *N,N*-dimethylcarbamate (**5a**; 1.388 g, 7.745 mmol) was treated successively with LDA (4.7 ml, 9.4 mmol), DPPCl (2.289 mg, 8.521 mmol), and NaN_3 (1.523 g, 23.43 mmol). The crude product was bulb-to-bulb distilled at 130°/$8 \cdot 10^{-2}$ mbar: 708 mg (45%) of **6a**. Colourless oil. IR (neat): 3060*w*, 3030*w*, 2930*m*, 2140*m*, 2100*s*, 1660*s*, 1600*w*, 1580*w*, 1495*m*, 1455*m*, 1420*m* (sh), 1400*m*, 1300*w*, 1250*m*, 1235*m*, 1180*w*, 1140*m*, 1080*w*, 1060*w*, 1000*w*, 970*w*, 910*w*, 875*m*, 840*w*, 775*w*, 760*w*, 720*m*, 710*m*, 625*m*, 610*m*. ^1H-NMR: 7.45–7.4 (*m*, 5 arom. H); 4.96 (*s*, PhC*H*N_3); 3.00, 2.81 (2*s*, Me_2N). ^{13}C-NMR: 168.8 (*s*, C=O); 133.8 (*s*, 1 arom. C); 129.4, 129.2, 128.0 (3*d*, 5 arom. CH); 63.7 (*d*, PhCHN$_3$); 36.8, 36.1 (2*q*, Me_2N). CI-MS: 205 (100, $[M + 1]^+$), 177 (41).

*α-Azido-*N,N*-diisopropylbenzeneacetamide* (**6b**). As in the previous experiment, benzyl *N,N*-diisopropylcarbamate (**5b**, 1.473 g, 6.259 mmol) was treated with LDA (3.75 ml, 7.5 mmol), DPPCl (1.860 g, 6.924 mmol) and NaN_3 (1.230 g, 18.92 mmol). CC (SiO_2, hexane/Et_2O 1:3) yielded 474 mg (29%) of **6b**, 615 mg (42%) of **5b**, and 374 mg (13%) of *[(diisopropylcarbamoyl)(phenyl)methyl]diphenyl phosphate* (**7**).

6b: Colourless crystals. M.p. 104–105°. IR: 3060*w*, 3020*m* (sh), 3000*s*, 2970*s*, 2960*m*, 2870*w*, 2440*w*, 2400*w*, 2100*s*, 1650*s*, 1585*w*, 1495*w*, 1470*m*, 1445*s*, 1380*m*, 1370*m*, 1340*m*, 1220*m*, 1180*w*, 1155*m*, 1145*m*, 1075*w*, 1040*m*, 1000*w*, 960*w*, 915*w*, 890*w*, 870*w*, 710*m*, 700*m*, 660*w*. ^1H-NMR: 7.45–7.25 (*m*, 5 arom. H); 4.87 (*s*, PhC*H*N_3); 3.71 (*sept.*, $J = 6.6$, Me_2CHN); 3.36 (*sept.*, $J = 6.8$, Me_2CHN); 1.48, 1.44 (2*d*, $J = 6.8$, Me_2CHN); 1.10, 0.65 (2*d*, $J = 6.6$, Me_2CHN). ^{13}C-NMR: 167.2 (*s*, C=O); 134.6 (*s*, 1 arom. C); 129.3, 129.0, 127.8 (3*d*, 5 arom. CH); 65.0 (*d*, PhCHN$_3$); 48.7, 46.5 (2*d*, $(Me_2CH)_2N$); 20.6, 19.8, 19.5 (3*q*, $(Me_2CH)_2N$). CI-MS: 261 (100, $[M + 1]^+$). Anal. calc. for $C_{14}H_{20}N_4O$ (260.34): C 64.59, H 7.74, N 21.52; found: C 64.43, H 7.86, N 21.69.

7: Colourless oil. IR: 3460*w*, 3010*w*, 2970*m*, 2930*m*, 2870*w*, 1720*w*, 1660*s*, 1590*m*, 1490*s*, 1450*m*, 1370*s*, 1345*m*, 1280*s*, 1180*m*, 1160*s*, 1140*w*, 1050*m*, 1025*s*, 1010*m*, 950*s*, 905*w*, 690*m*, 605*w*. ^1H-NMR: 7.4–7.0 (*m*, 15 arom. H); 6.14 (*d*, $J = 8.0$, PhC*H*OP(O)(OPh)$_2$); 3.85 (*sept.*, $J = 6.6$, Me_2CHN); 3.31 (*sept.*, $J = 6.8$, Me_2CHN); 1.43, 1.36 (2*d*, $J = 6.8$, Me_2CHN); 1.00, 0.70 (2*d*, $J = 6.6$, Me_2CHN). ^{13}C-NMR: 165.3 (*s*, C=O); 150.5, 150.3, 135.1 (3*s*, 3 arom. C); 129.7, 129.6, 129.1, 128.9, 127.5, 125.3, 125.2, 120.5, 120.2 (9*d*, 15 arom. CH); 79.1 (*d*, PhCHOP(O)(OPh)$_2$); 48.2, 46.4 (2*d*, $(Me_2CH)_2N$); 20.5, 19.7, 19.5 (3*q*, $(Me_2CH)_2N$). CI-MS: 469 (26), 468 (100, $[M + 1]^+$), 218 (42, $[M - OP(O)(OPh)_2]^+$).

2-Azido-2-phenyl-1-(piperidin-1-yl)ethanone (= *1-[Azido(phenyl)acetyl]piperidine*; **6c**). *a*) As in the previous experiment, benzyl piperidine-1-carboxylate (**5c**; 1.606 g, 7.324 mmol) was treated with LDA (4.0 ml, 8.0 mmol), DPPCl (1.65 ml, 8.0 mmol), and NaN_3 (1.428 g, 21.96 mmol). CC (SiO_2, hexane/AcOEt 2:1) yielded 603 mg (34%) of **6c** and 457 mg (28%) of **5c**. **6c**: Pale yellow oil. B.p. 170°/$8 \cdot 10^{-2}$ mbar. IR (neat): 3080*w*, 3020*w*, 3000*w*,

2940*m*, 2860*m*, 2100*s*, 1650*s*, 1600*w*, 1585*w*, 1490*m*, 1455*s* (sh), 1445*s*, 1370*w*, 1350*w*, 1300*w*, 1280*m*, 1270*m*, 1245*m*, 1220*s*, 1180*w*, 1160*w*, 1140*m*, 1125*w*, 1080*w*, 1020*m*, 960*m*, 915*m*, 870*m*, 850*m*, 810*w*, 770*w*, 760*w*, 715*m*, 700*m*, 670*w*. ^{1}H-NMR: 7.45–7.35 (*m*, 5 arom. H); 4.99 (*s*, PhC*H*N_3); 3.8–3.7, 3.5–3.4, 3.2–3.15 (3*m*, CH_2NCH_2); 1.6–1.45, 1.35–1.2, 1.0–0.95 (3*m*, 3 CH_2). ^{13}C-NMR: 166.7 (*s*, C=O); 134.2 (*s*, 1 arom. C); 129.2, 129.0, 127.7 (3*d*, 5 arom. CH); 63.9 (*d*, PhCHN$_3$); 46.4, 43.4 (2*t*, C(2), C(6) of piperidine); 25.5, 25.3, 24.1 (3*t*, C(3), C(4), C(5) of piperidine). CI-MS: 245 (100, $[M + 1]^+$), 219 (24), 217 (77), 85 (24), 71 (31), 69 (34).

b) To a soln. of **5c** (1.609 g, 7.338 mmol) in THF (20 ml) at 0°, 2M LDA in THF (4.0 ml, 8.0 mmol) was added slowly. After stirring for 2 h at 0°, diphenyl phosphorazidate (DPPA; 1.75 ml, 8.1 mmol) was added and the mixture stirred for 3 days at r.t. The precipitate was removed by filtration and the solvent evaporated. The residue was dissolved in CH_2Cl_2 and washed with 5% $NaHCO_3$ soln. The combined aq. phase was extracted with CH_2Cl_2 and the org. phase dried ($MgSO_4$) and evaporated. CC (SiO_2, hexane/Et_2O 2:1) gave 600 mg (33%) of **6c** and 376 mg (23%) of **5c**.

2. *Dipeptides from Azido-amides* **6**. *α-{{2-{[(Benzyloxy)carbonyl]amino}ethanoyl}amino}-N,N-dimethylbenzeneacetamide* (**10**). *a*) A soln. of **6a** (37 mg, 0.181 mmol) and Bu_3P (techn. 85%; 55 µl, 0.19 mmol) in dry toluene (1 ml) was stirred at r.t. (slow N_2 evolution). After 4 h, Z-Gly-OH (38 mg, 1.182 mmol) was added and the mixture heated to 80° for 8 h. Then, CH_2Cl_2 was added, the soln. washed with 10% $NaHCO_3$ soln., brine, and 1N HCl, and the aq. layers were extracted with CH_2Cl_2. The combined CH_2Cl_2 phase was dried ($MgSO_4$) and evaporated and the residue recrystallized from AcOEt: 38 mg (57%) of **10**. Colourless crystals. M.p. 162–163°. IR: 3400*w* (br.), 3030*w* (sh), 3000*m*, 2840*w*, 1730*m*, 1690*m* (sh), 1680*m*, 1660*m* (sh), 1650*s*, 1495*s*, 1470*m* (sh), 1455*m*, 1415*m*, 1405*m*, 1335*w*, 1250*m*, 1150*m*, 1090*w*, 1050*w*, 920*w*. ^{1}H-NMR: 7.51 (br. *d*, *J* = 6.9, 1 NH); 7.4–7.25 (*m*, 10 arom. H); 5.83 (*d*, *J* = 7.3, PhC*H*); 5.55–5.45 (br. *m*, 1 NH); 5.09 (*s*, PhCH_2O); 3.95–3.8 (*m*, NHCH_2CO); 2.97, 2.88 (2*s*, Me_2N). ^{13}C-NMR: 169.3, 167.7 (2*s*, 2 C=O); 156.3 (*s*, OCONH); 136.8, 136.2 (2*s*, 2 arom. C); 129.0, 128.4, 128.3, 128.0, 127.9, 127.8 (6*d*, 10 arom. CH); 67.0 (*t*, PhCH_2O); 53.9 (*d*, PhCH); 44.2 (*t*, NHCH_2CO); 36.8, 35.9 (2*q*, Me_2N). CI-MS: 371 (19), 370 (91, $[M + 1]^+$), 262 (100, $[M - PhCH_2O]^+$). Anal. calc. for $C_{20}H_{23}N_3O_4$ (369.42): C 65.02, H 6.27, N 11.37; found: C 64.86, H 6.28, N 11.36.

b) A suspension of **6a** (35 mg, 0.171 mmol) and 5% Pd/C (5 mg) in abs. MeOH (1 ml) was stirred for 1 h under H_2. Then, the catalyst was removed by filtration through a *Celite* pad and the solvent evaporated. The residue was dissolved in CH_2Cl_2, and Z-Gly-OH (45 mg, 0.215 mmol), *O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-bis (tetramethylene)uronium hexafluorophosphate (HBPyU; 91 mg, 0.221 mmol), and Et_3N (30 µl, 0.215 mmol) were added. After stirring the soln. for 16 h at r.t., it was washed twice with 1N HCl, and the aq. layers were extracted with CH_2Cl_2. The org. phase was dried ($MgSO_4$) and evaporated. FC (SiO_2, AcOEt/hexane 7:1) and crystallization from AcOEt yielded 44 mg (69%) of **10**. Colourless crystals.

N²-[(Benzyloxy)carbonyl]-N¹,N¹-dimethylglycinamide (Z-Gly-NMe_2; **11**). To an ice-cooled soln. of **6c** (35 mg, 0.143 mmol) in toluene (1 ml), hexamethylphosphorous triamide (26 µl, 0.160 mmol) was added and the mixture stirred for 1 h at r.t. Then, Z-Gly-OH (34 mg, 0.162 mmol) was added and the mixture heated to 80°. After 8 h, CH_2Cl_2 was added, the soln. washed with 10% $NaHCO_3$ soln., brine, and 1N HCl, and the H_2O layers were extracted with CH_2Cl_2. The org. phase was dried ($MgSO_4$) and evaporated and the residue purified by FC (AcOEt/hexane 7:1): 20 mg (59%) of **11**. Colourless solid. ^{1}H-NMR: 7.3–7.2 (*m*, 5 arom. H); 5.74 (br. *s*, 1 NH); 5.05 (*s*, PhCH_2O); 3.93 (*d*, *J* = 4.2, CH_2 of Gly); 2.91, 2.89 (2*s*, Me_2N). ^{13}C-NMR: 167.8 (*s*, C=O); 156.1 (*s*, OCONH); 136.4 (*s*, arom. C); 128.4, 128.0, 127.9 (3*d*, 5 arom. CH); 66.7 (*t*, PhCH_2O); 42.6 (*t*, CH_2 of Gly); 35.7, 35.5 (2*q*, Me_2N). ESI-MS: 275 (14, $[M + K]^+$), 260 (13), 259 (100, $[M + Na]^+$), 237 (29, $[M + 1]^+$).

Crystal Structure Determination of **6b** (see *Table* and *Fig.*)[5]). The intensities were collected on a *Rigaku-AFC5R* diffractometer using graphite-monochromated MoK_α radiation (λ 0.71069 Å) and a 12-kW rotating anode generator. The intensities were corrected for *Lorentz* and polarization effects, but not for absorption. Data collection and refinement parameters are listed in the *Table*, and a view of the molecule is shown in the *Figure*. The structure was solved by direct methods using SHELXS86 [13], which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. All of the H-atoms were located in a difference electron density map, and their positions were allowed to refine together with individual isotropic displacement parameters. All refinements were carried out on *F* using full-matrix least-squares procedures. A correction for secondary

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[5]) Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication No. CCDC-10/57. Copies of the data can be obtained, free of charge, on application to the Director, *CCDC*, 12 Union Road, Cambridge CB2 1EZ, UK (fax: + 44-091223-336033; or email: teched@-ccdc.cam.ac.uk).

Table. *Crystallographic Data of Compound* **6b**

Crystallized from	$CHCl_3$/hexane	D_x [g cm^{-3}]	1.206
Empirical formula	$C_{14}H_{20}N_4O$	$\mu(MoK_\alpha)$ [mm^{-1}]	0.0793
Formula weight	260.34	Scan type	$\omega/2\theta$
Crystal colour, habit	colourless, prism	$2\theta_{(max)}$ [°]	55
Crystal dimensions [mm]	$0.30 \times 0.33 \times 0.50$	Total reflections measured	3660
Temperature [K]	173(1)	Symmetry-independent reflections	3287
Crystal system	monoclinic	Reflections used [$I > 2\sigma(I)$]	2459
Space group	$P2_1/n$	Parameters refined	253
Z	4	Final R	0.0508
Reflections for cell determination	25	wR ($w = [\sigma^2(F_o) + (0.005F_o)^2]^{-1}$)	0.0457
2θ range for cell determination [°]	37–40	Goodness of fit	2.097
Unit cell parameters a[Å]	9.295(3)	Secondary extinction coefficient	$9.0 \cdot 10^{-7}$
b[Å]	11.401(3)	Final Δ_{max}/σ	0.0004
c[Å]	13.772(2)	$\Delta\rho$ (max; min) [e Å^{-3}]	0.28; −0.23
β[°]	100.77(2)	Range of $\sigma(d(C-C))$ [Å]	0.002–0.003
V[Å^3]	1433.8(6)		

extinction was applied. Neutral-atom scattering factors for non-H-atoms were taken from [14a] and the scattering factors for H-atoms from [15]. Anomalous dispersion effects were included in F_{calc} [16]; the values for f' and f'' were those of [14b]. All calculations were performed using the TEXSAN crystallographic software package [17].

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